



A Teaching Affiliate
of Harvard Medical School

Update in GI Malignancy 2022

Themes to Know

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Disclosures June 2022

- Equity
 - MPM Capital, Acworth Pharmaceuticals, Exact Science
- Advisor
 - MPM Capital, Gritstone Oncology, Oncorus, TCR2, Maverick Therapeutics. Exact Sciences/Thrive Earlier Detection
- Publishing
 - Uptodate, McGraw Hill, Johns Hopkins University Press
- Research
 - SU2C



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Objectives

- Colorectal Cancer 2022:
 - Total neoadjuvant therapy
 - Immunotherapy gets a foothold
- Pancreatic Cancer 2022
 - BRCA mutant disease
 - Movement to preoperative
 - CAR-T?
- GE Cancer 2022
 - HER2
 - Immunotherapy postop and first line metastatic



Workup of newly diagnosed colon cancer

- Symptoms leading to colonoscopy OR baseline screening colonoscopy identifies lesion
- **PATH MUST INCLUDE STAINING FOR MMR (Lynch Syndrome and Immunotherapy)**
- Obtain baseline serum CEA
- Obtain Staging CT [chest] abdomen/pelvis
- Colon: Is it localized? Resectable? To the OR!
- Rectal: is it localized? WAIT...THINK Preoperative Rx



Colon Cancer Treatment

- Step 1: Surgery to remove tumor.
- Step 2: Pathologic staging of tumor to determine next steps.
 - Stage I (T1/2,N0): surgery (Laparoscopic, Robotic, or open)
 - Stage II (T3/4,N0): surgery + ?chemotherapy
 - Stage III (T_{any},N+): surgery + chemotherapy
 - Stage IV (T_{any} N_{any},M1): chemotherapy + ?surgery. (Patients with isolated liver or lung metastases can be cured with surgical resection (M1a))



How to Explain to Patients: Stage IIc

- In general...assume a 30% relative benefit for chemotherapy

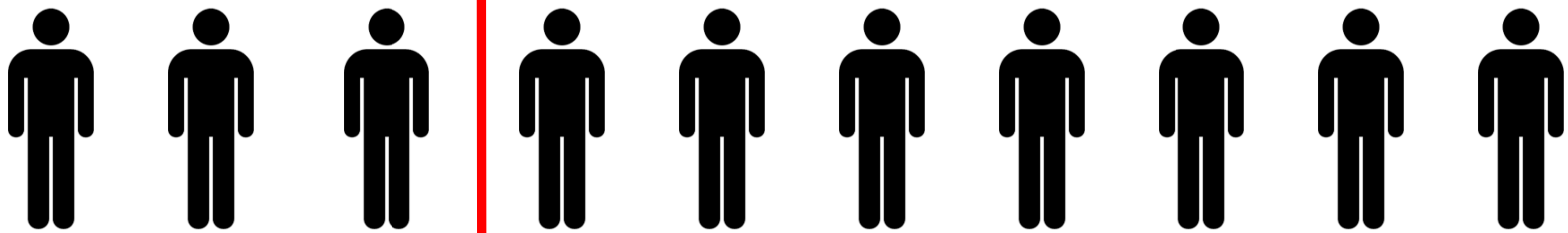


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How to Explain to Patients: Stage IIIc

- In general...assume a 30% relative benefit for chemotherapy

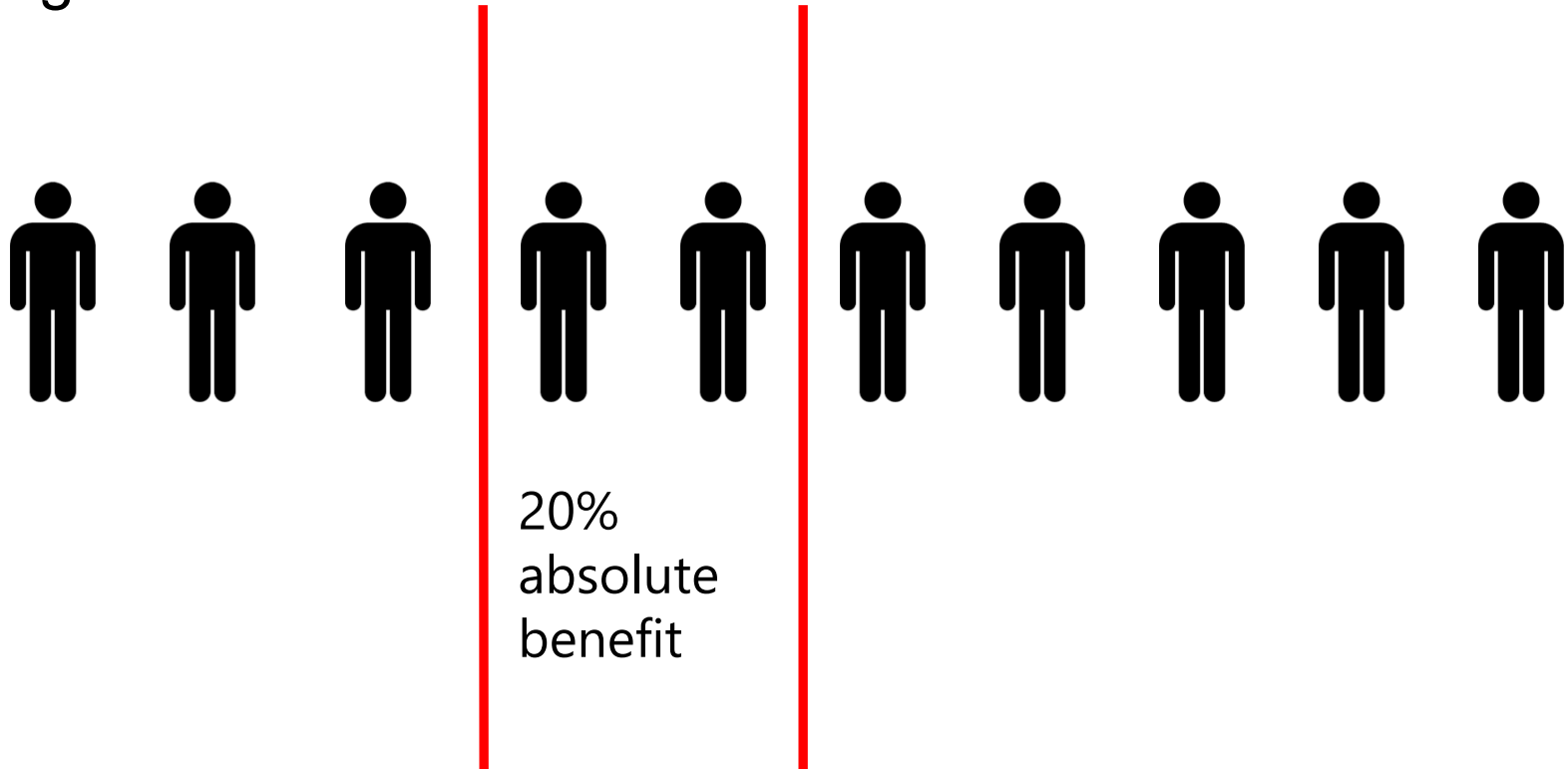


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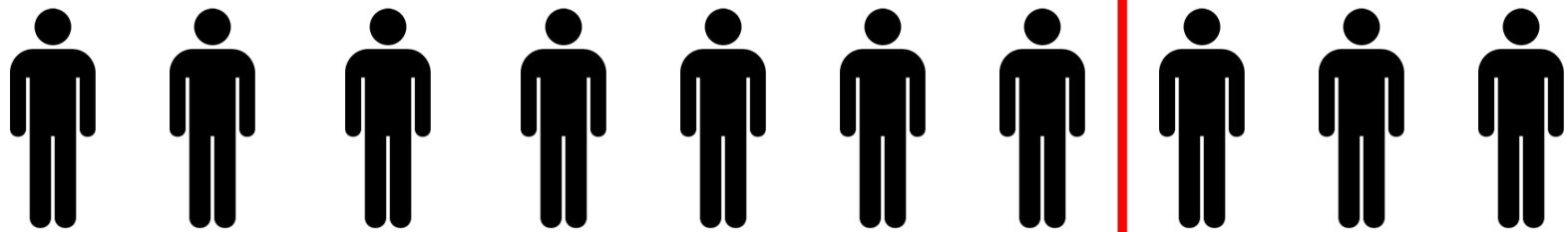
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How to Explain to Patients: Stage IIIc

- In general...assume a 30% relative benefit for chemotherapy



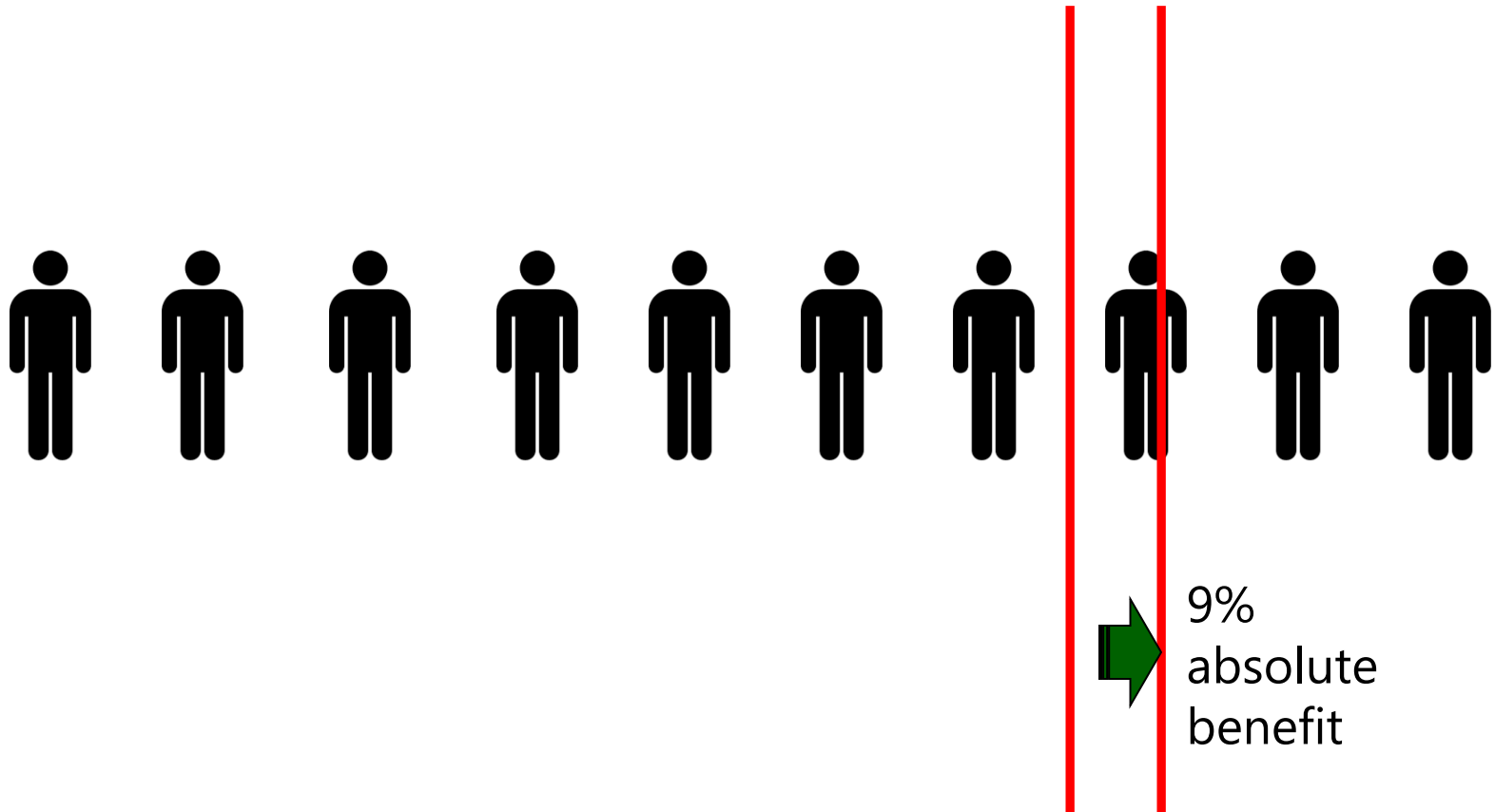
How to Explain to Patients: Stage IIIa



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How to Explain to Patients: Stage IIIa

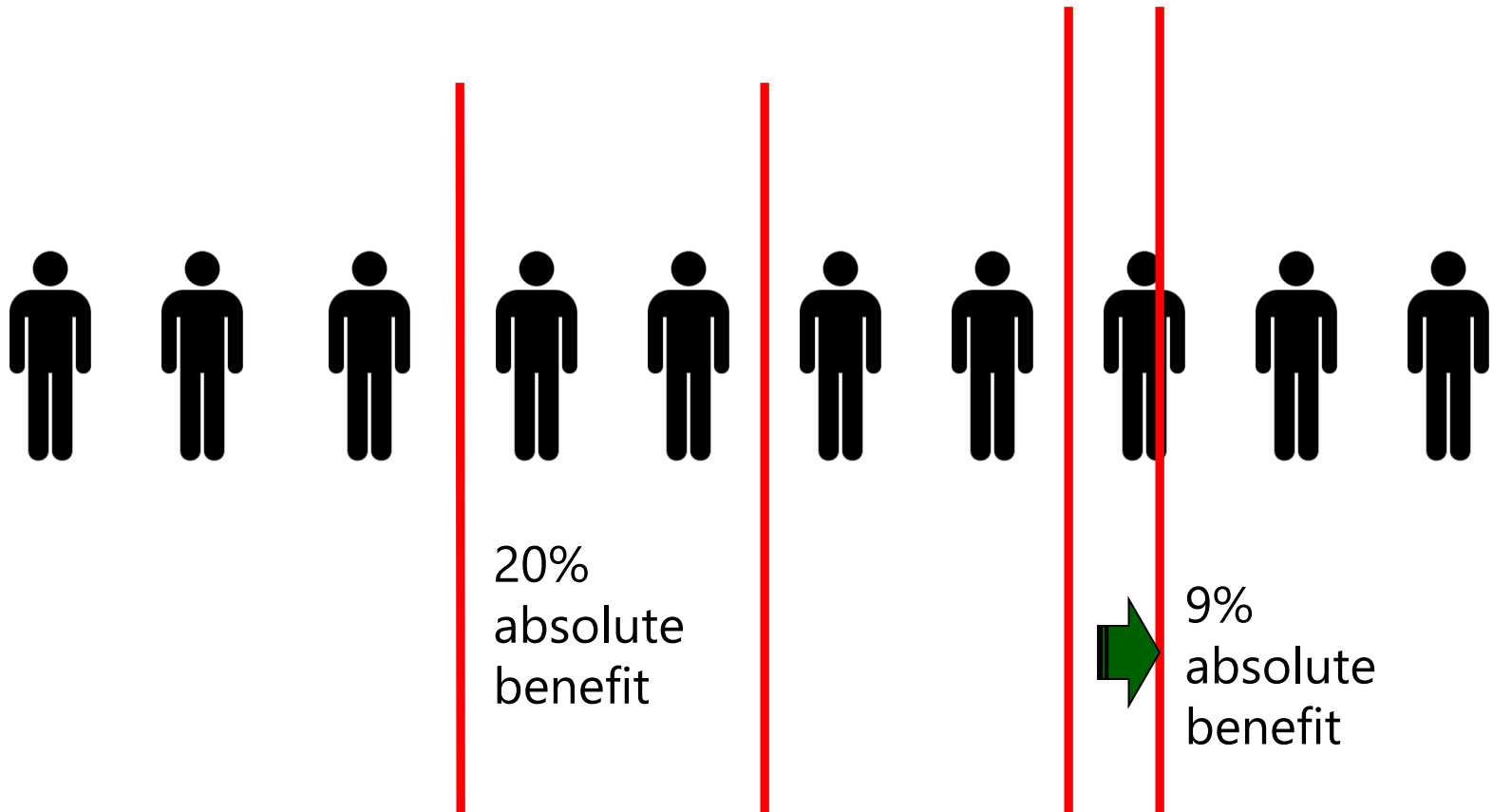


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How to Explain to Patients: Stage IIIc v IIIa

A very different value proposition



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Rectal Cancer Treatment

- *Clinical* Stage I: surgery alone
- *Clinical* Stage II: chemotherapy + radiation + surgery
- *Clinical* Stage III: chemotherapy + radiation + surgery
- *Clinical* Stage IV: chemotherapy + ?surgery (Patients with isolated liver or lung metastases can be cured with staged surgical resection (M1a))



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Rectal Cancer: The Changing Paradigm

- A balancing act between local control, systemic control, and life-long morbidity from surgery and radiation



Rectal Cancer: The Changing Paradigm

- A balancing act between local control, systemic control, and life-long morbidity from surgery and radiation

- WAIT A SEC...NO SURGERY???

4-6m Chemotherapy

CMT or XRT



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Rectal Cancer Treatment

- Surgery not necessary in patients with a complete response to TNT (total neoadjuvant therapy).
- 20-30% of patients will have a complete clinical response to total neoadjuvant therapy (approx. 6m of chemo and some form of radiation)
- Approximately 20% of patients will have local regrowth
- Very few patients develop metastases without local regrowth first
- Very specialized care (every three month flex sig and MRI, and every 6m CTs for about 3 years)



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Colorectal Cancer Metastases

Key Take-home Messages

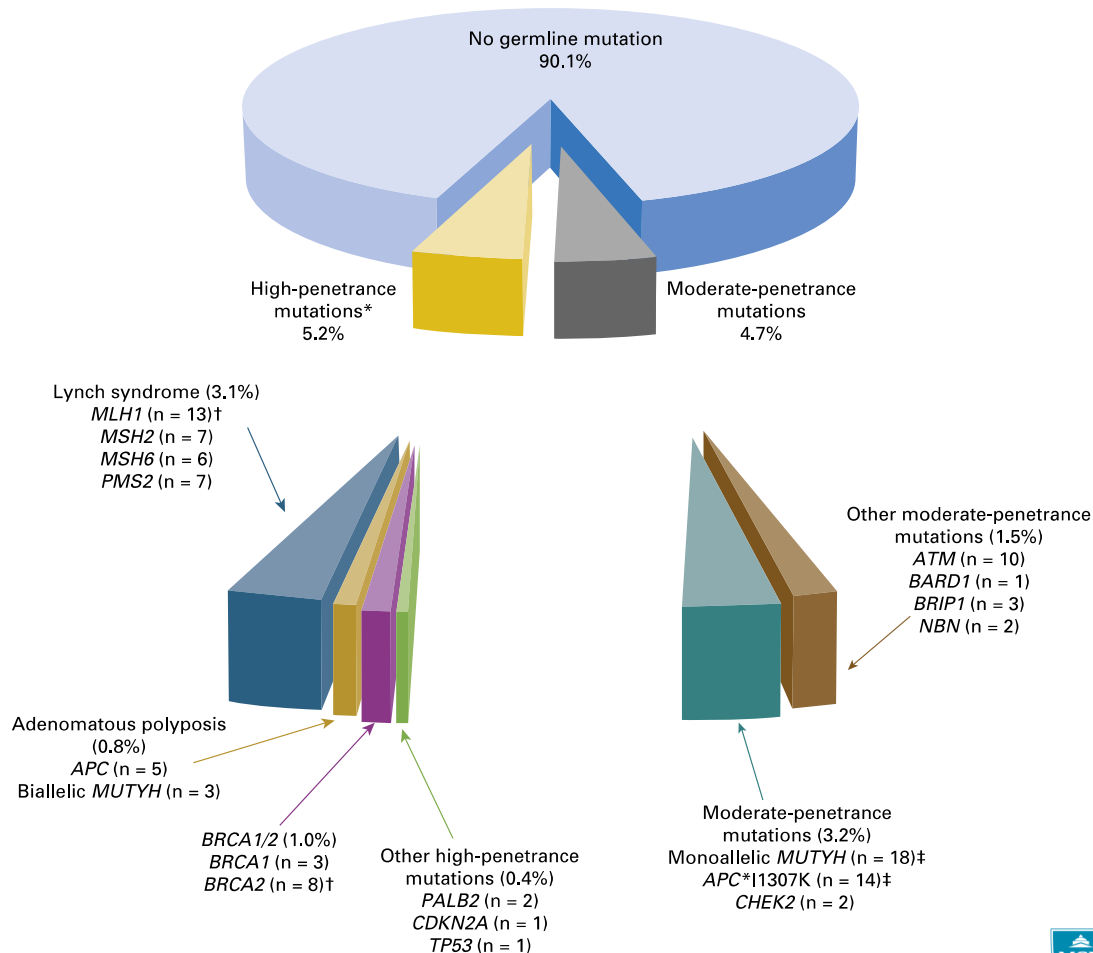
- Metastatic disease can be cured
- About 10% of patients will have an inherited predisposition...while the guidelines have not caught up to practice, most of us are telling all patients to get germline testing
- Approx 25% of patients are living for 5+ years on and off chemotherapy



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Inherited Predisposition to Colon cancer



Yurgelun et al JCO 2017



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Colorectal Cancer Surveillance

- Colonoscopy 1 year after diagnosis and then every 3-5 years
- For stage II and III, every 3 month CEA/physical exam and annual CT for 3 years.
- Then, follow annually with CEA and LFTs until year 5
- Lifestyle/Dietary Changes: Very good retrospective and/or observational evidence
 - Exercise, ASA, Vitamin D
 - Mediterranean diet
- High Risk Genetics Work

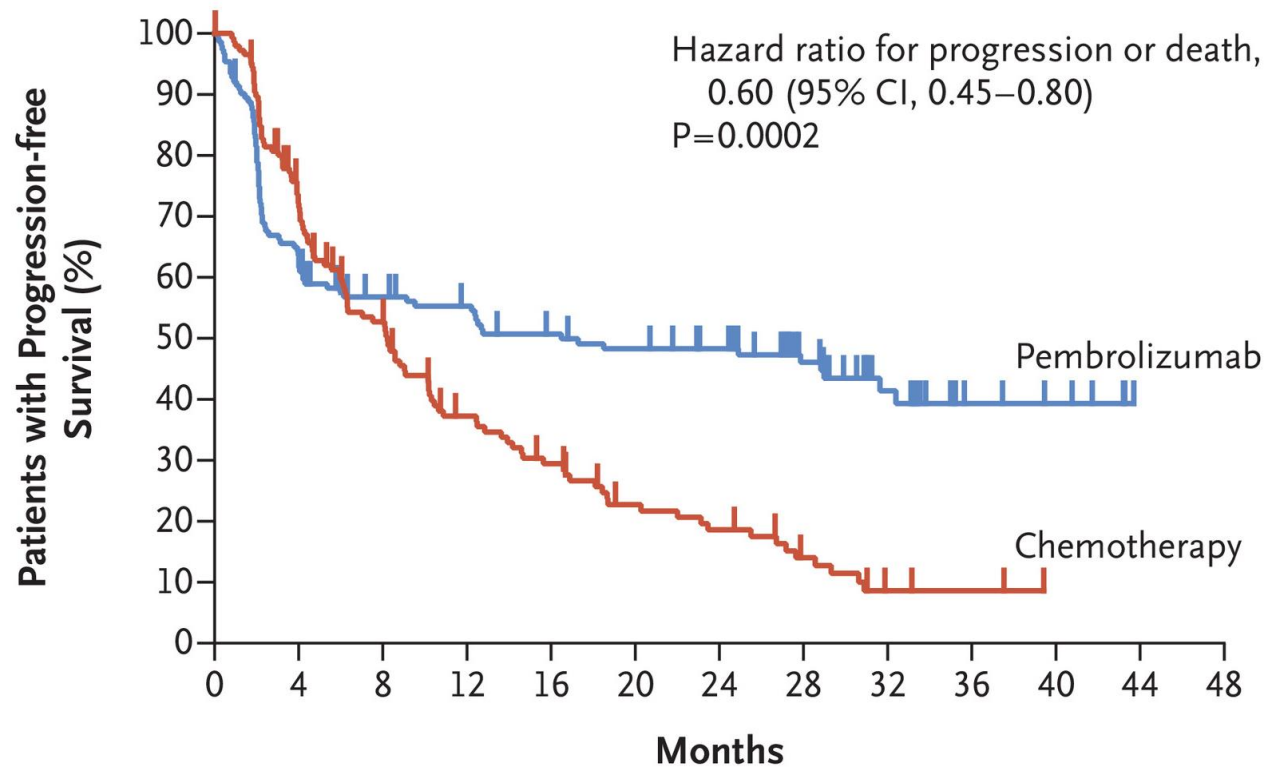


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Immunotherapy and colon cancer

- 1st line IO is much better than chemo for patients with MSI high disease



- Shiu et al
NEJM 2020

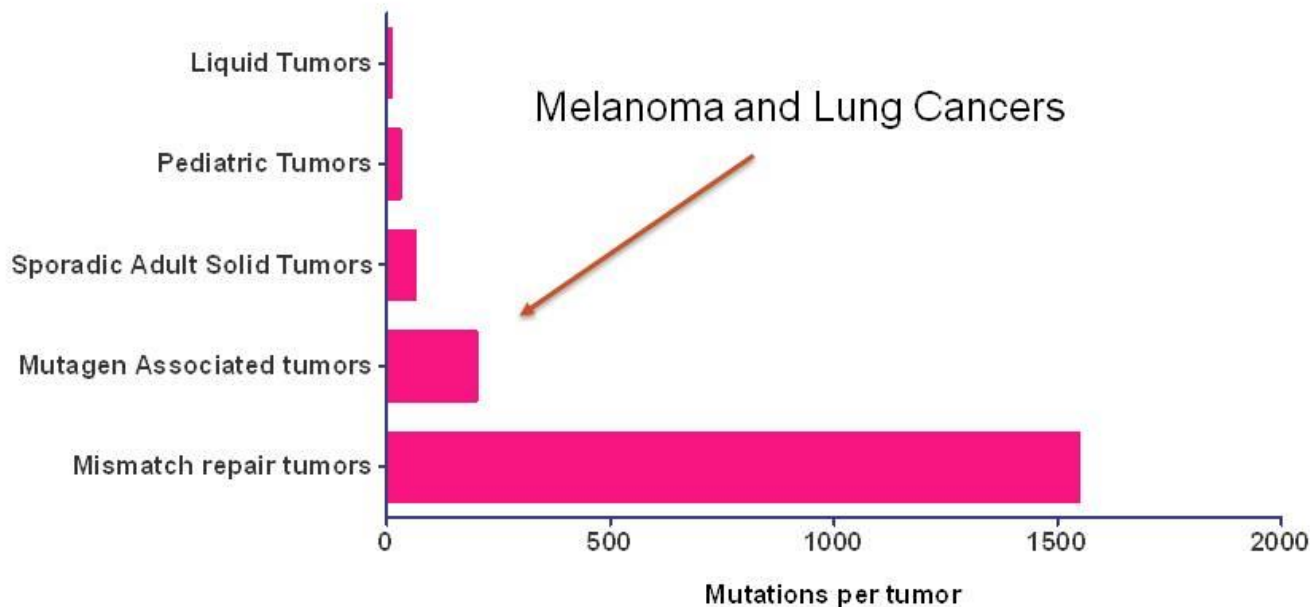


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High “Mutational Load” in mismatch repair-deficient tumors

Mutations per tumor



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PRESENTED AT:

ASCO Annual Meeting 2015



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Immunotherapy Complications

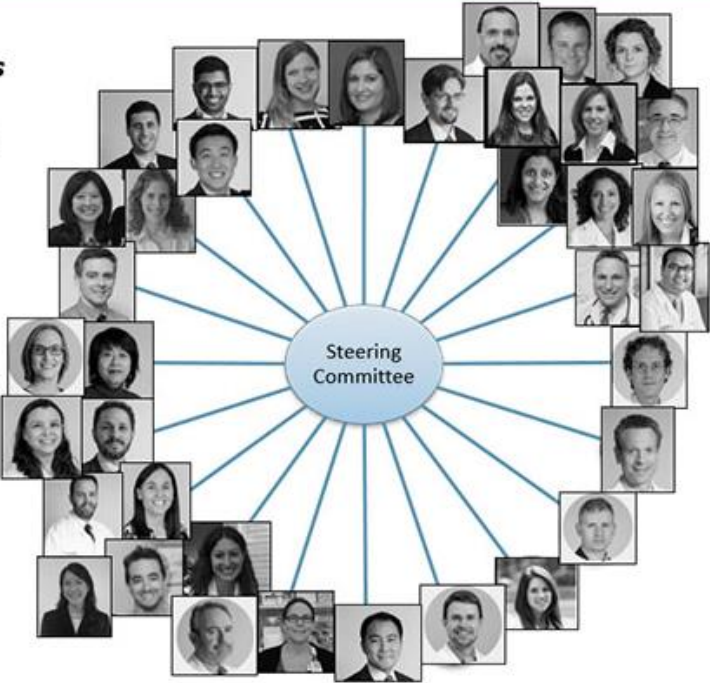


Immunotherapy Toxicity Service



51 members
across 6
departments
and 10
divisions of
Medicine

15 members
actively
bridging
between
clinical and
laboratory
work



Gathering experts & champions across division of medicine

Objectives

- Colorectal Cancer 2021:
 - Total neoadjuvant therapy
 - Immunotherapy gets a foothold
- Pancreatic Cancer 2021
 - BRCA mutant disease; up to 5% of patients may have inherited a BRCA mutation
 - Movement to preoperative
- GE Cancer 2021
 - HER2
 - Immunotherapy postop and first line metastatic

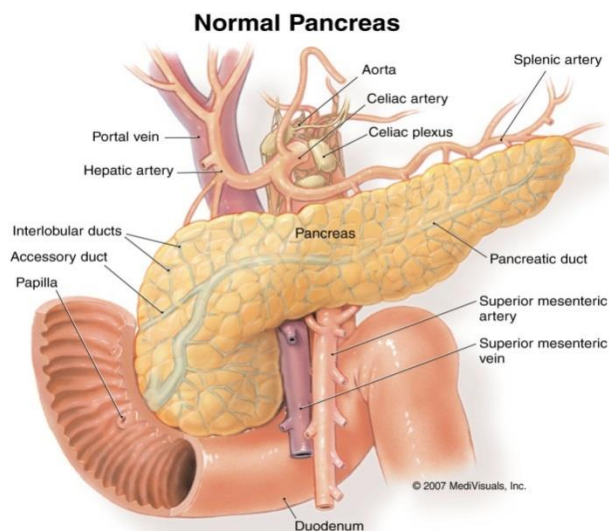
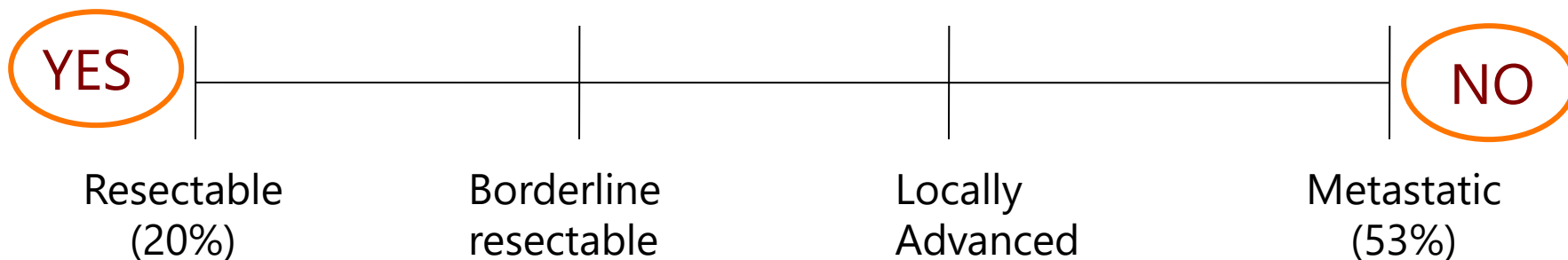


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How Oncologists Think About Pancreatic Cancer

Can the cancer be taken out with a surgery?



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Pancreatic Cancer

Things to know

- Local disease can be cured
- BRCA mutant or BRCA-like tumors
 - 5-10% of patients will have germline + somatic mutations of BRCA like genes
- MSI occurs in about 1%
- Germline: testing is now recommended by NCCN for any patient with confirmed pancreatic cancer using comprehensive gene panels for hereditary cancer syndromes

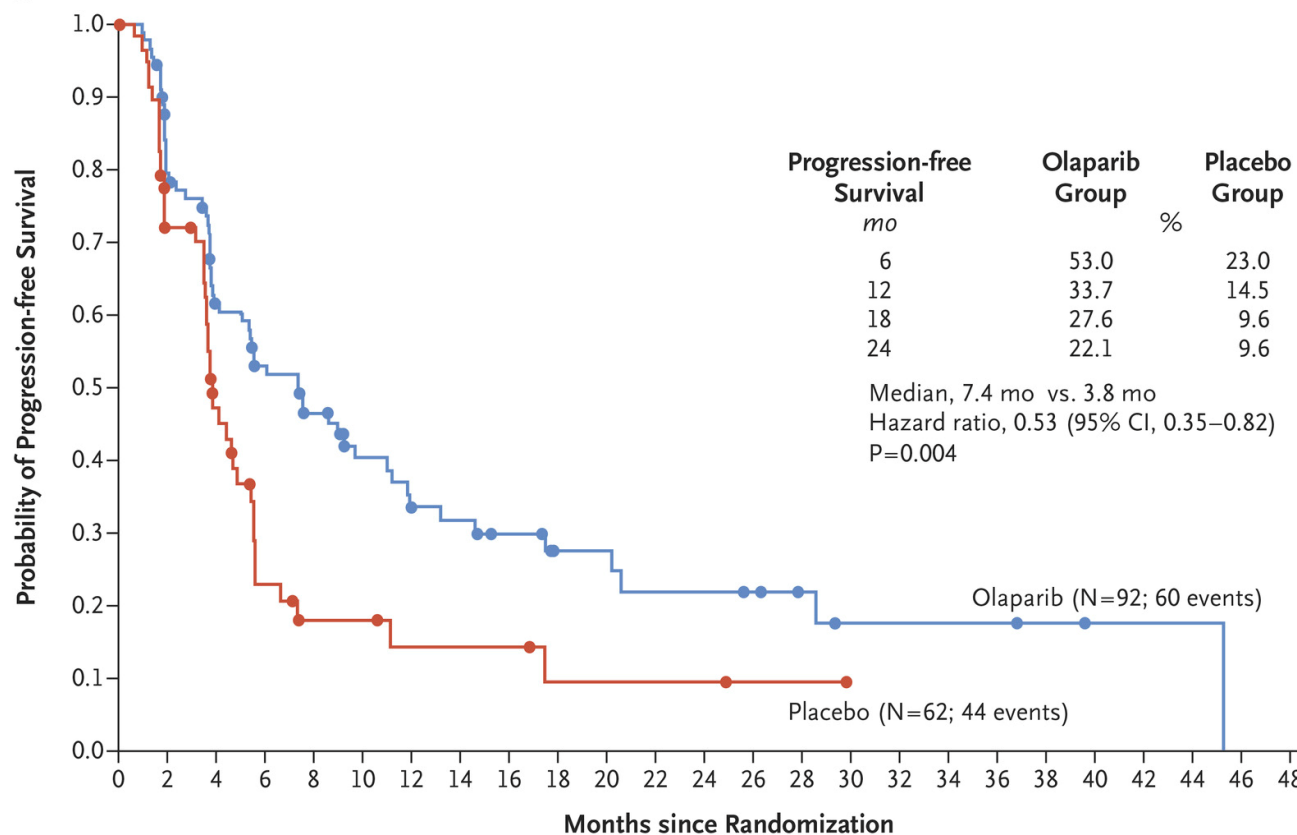


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BRCA Mutant Pancreatic Cancer

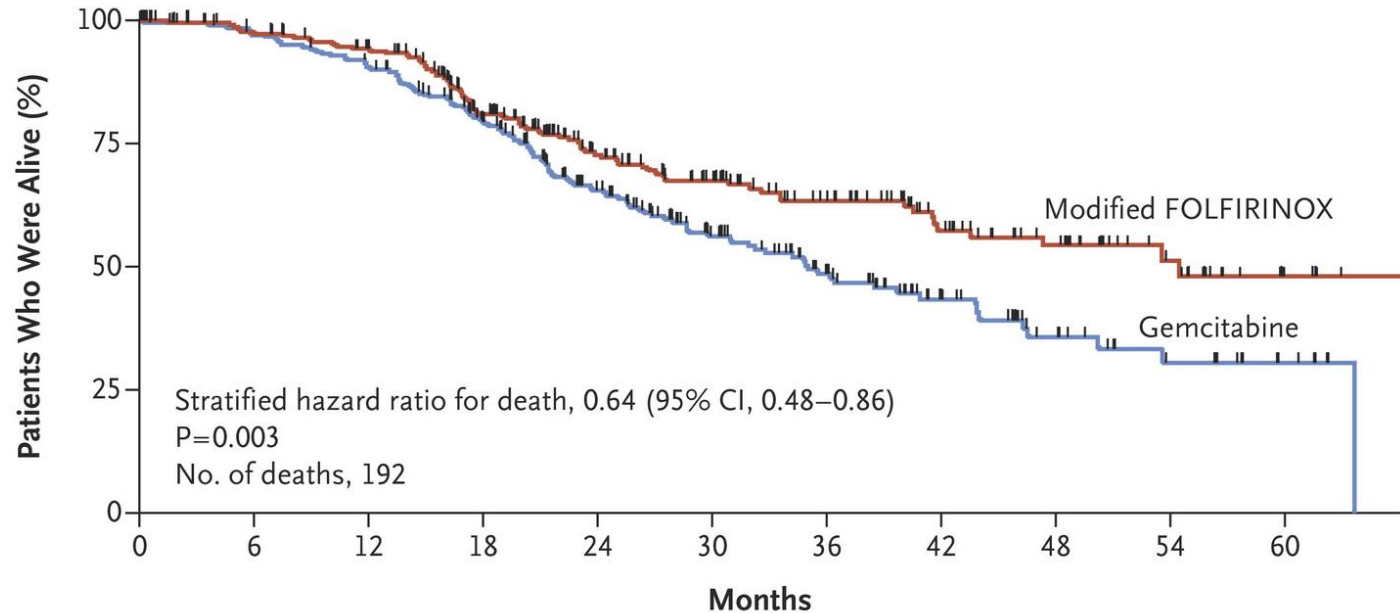
Progression-free Survival



Golan NEJM 2019

Pancreatic Cancer: Adjuvant Therapy

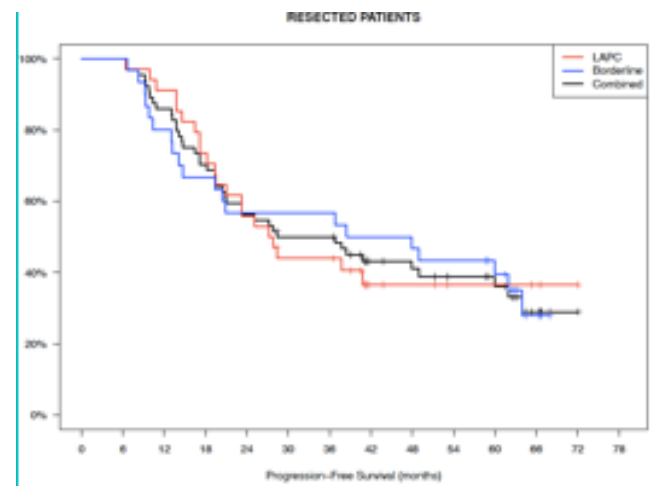
FOLFIRINOX improves OS



Conroy et al NEJM 2018

Locally Advanced Pancreatic Cancer – MGH Experience

- 97 patients treated with TNT followed by surgical resection
- 66 patients resected
- Median survival for R0 = 43m
- Ryan et al ASCO 2021



	N	mOS (mos)	LR only	LR+M	M alone	DwD nos	DwoD	NED
All	97	32.3	16	7	40	2	6	26
Unresected*	31	14.5	8	3	14	1	2	3
R0+R1	66	43.8	8	4	26	1	4	23
R0	61	43.8	7	4	24	1	3	22
R1	5	46.0	1	0	2	0	1	1

Recent Hope with T Cell Therapy

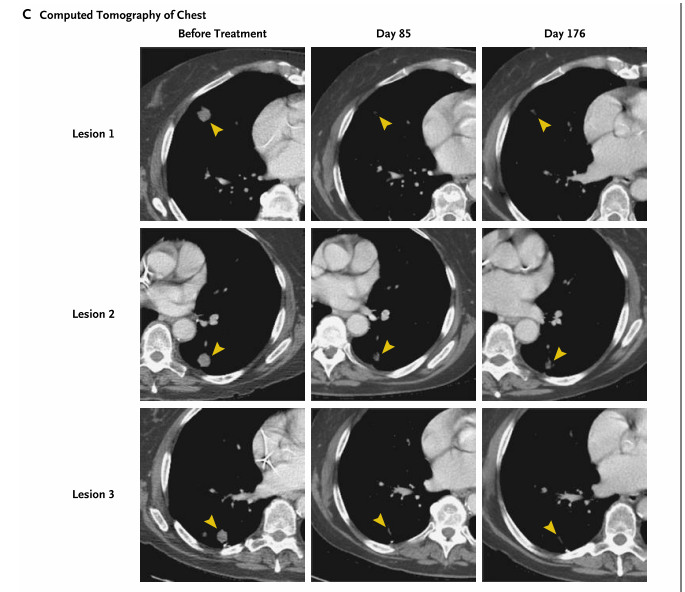
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Neoantigen T-Cell Receptor Gene Therapy in Pancreatic Cancer

Rom Leidner, M.D., Nelson Sanjuan Silva, B.S., Huayu Huang, M.S.,
David Sprott, B.S., Chunhong Zheng, Ph.D., Yi-Ping Shih, Ph.D., Amy Leung, B.S.,
Roxanne Payne, M.N., Kim Sutcliffe, B.S.N., Julie Cramer, M.A.,
Steven A. Rosenberg, M.D., Ph.D., Bernard A. Fox, Ph.D.,
Walter J. Urba, M.D., Ph.D., and Eric Tran, Ph.D.

- Autologous T cells engineered with TCRs against kras g12d HLA C 0802



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- Gastroesophageal Cancer
 - HER2: anti-HER2 therapy is incorporated into the care of patients with HER2 amplification
 - Early adoption of IO

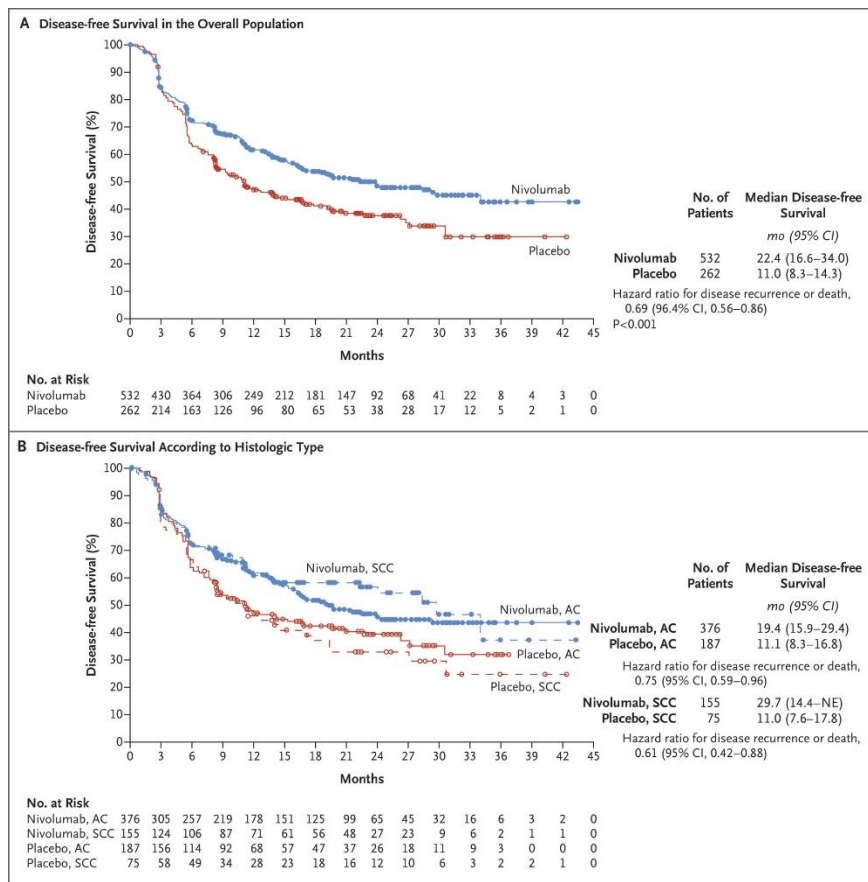


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GE Cancer: Immunotherapy works in local disease

- Chemoradiation followed by surgery followed by 6m of adjuvant Nivolumab is the new standard of care
- Early introduction of immunotherapy for both adjuvant and metastatic disease
- Kelly NEJM 2021



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Summary

- Germline testing is now recommended for nearly all patients with GI cancers
- Immunotherapy has profound effects in Microsatellite high or mismatch repair deficient patients
- There is a movement towards total neoadjuvant therapy for pancreas and rectal cancer



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Appendix Immuno Primer

Microsatellite Instability

- A change that occurs in the DNA of certain cells (such as tumor cells) in which the number of repeats of microsatellites (short, repeated sequences of DNA) is different than the number of repeats that was in the DNA when it was inherited. The cause of microsatellite instability may be a defect in the ability to repair mistakes made when DNA is copied in the cell. Also called MSI-high.
- It identifies a condition of genetic hypermutability (predisposition to mutation) that results from impaired DNA mismatch repair (MMR). The presence of MSI represents phenotypic evidence that MMR is not functioning normally.



Microsatellite Instability

- The condition of MSI can occur through ***mutation (less common) or silencing through methylation (more common)*** of the genes that encode mismatch repair proteins

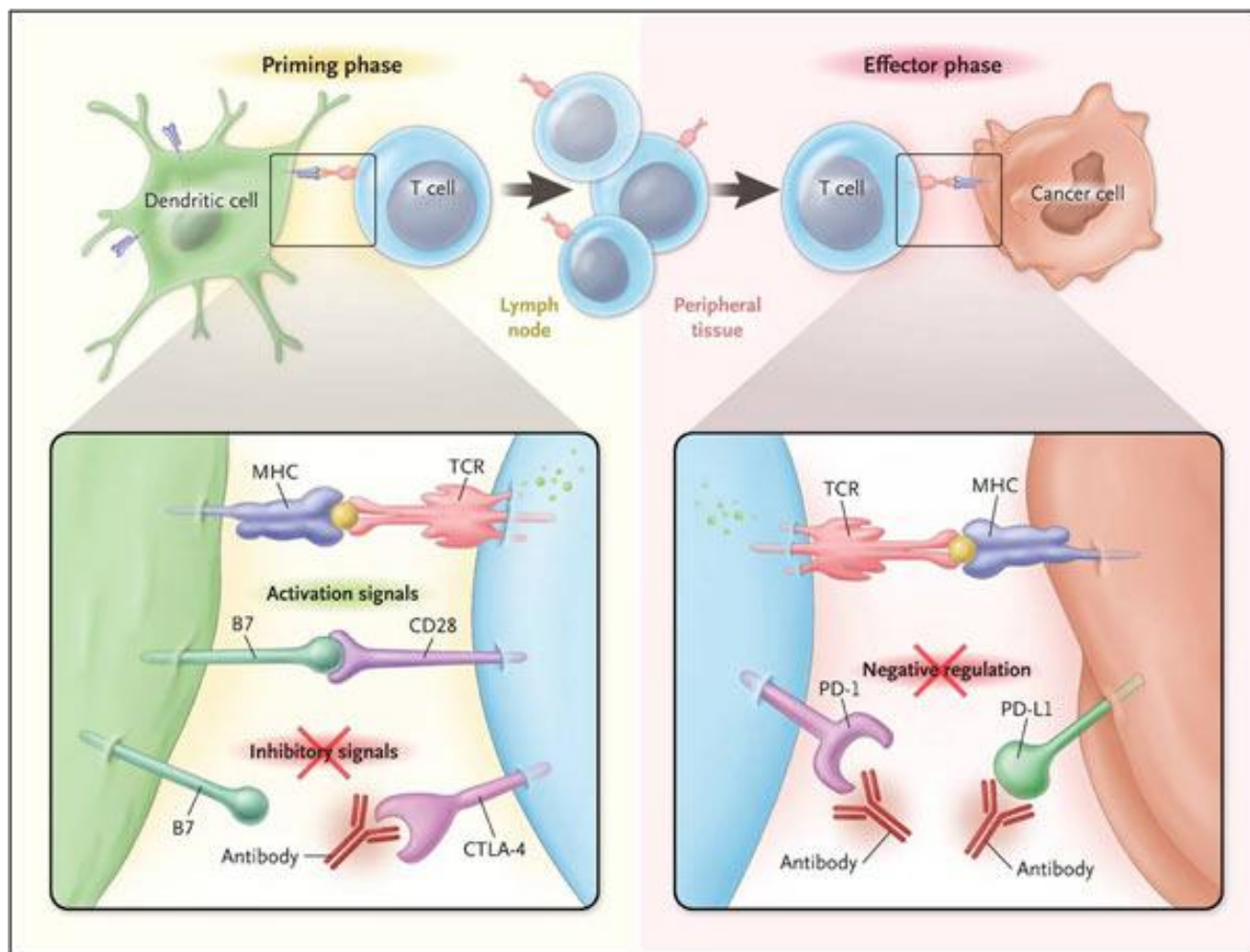
Lynch Syndrome (HNPCC):

- Variations in the [MLH1](#), [MSH2](#), [MSH6](#), [PMS2](#), or [EPCAM](#) gene increase the risk of developing Lynch syndrome.
- The *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes are involved in the repair of errors that occur when DNA is copied in preparation for cell division (a process called [DNA replication](#)). Mutations in any of these genes prevent the proper repair of DNA replication errors. As the abnormal cells continue to divide, the accumulated errors can lead to uncontrolled cell growth and possibly cancer.
- Mutations in the *EPCAM* gene also lead to impaired DNA repair, although the gene is not itself involved in this process. The *EPCAM* gene lies next to the *MSH2* gene on [chromosome 2](#); certain *EPCAM* gene mutations cause the *MSH2* gene to be turned off (inactivated), interrupting DNA repair and leading to accumulated DNA errors.
- Although mutations in these genes predispose individuals to cancer, not all people who carry these mutations develop cancerous tumors.



Is there a role for checkpoint inhibitors in GI Malignancies?

Checkpoint inhibitors



- Anti-CTLA-4
- Anti-PD-1
- Anti-PD-L1

Tested as single agents and in combination in pancreas cancer in ongoing trials

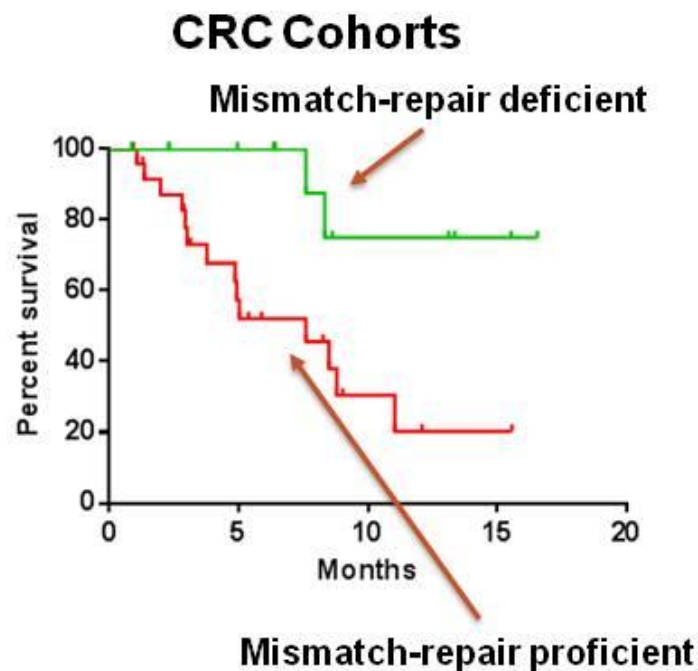
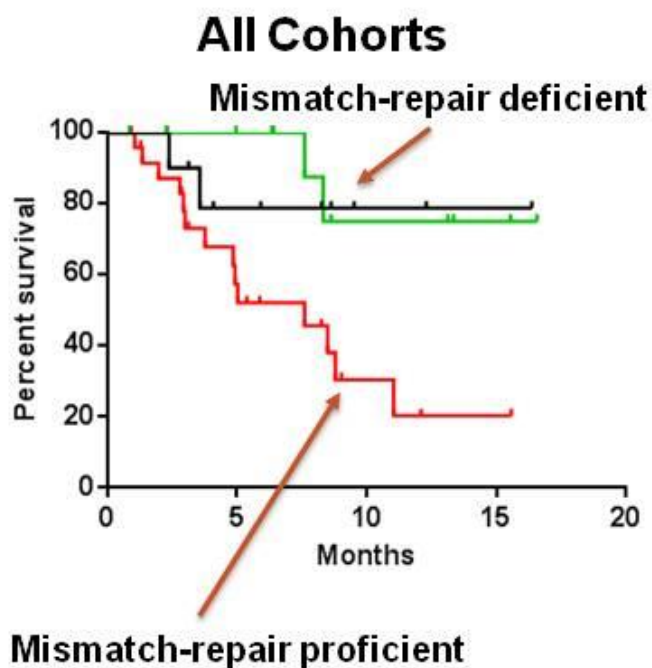


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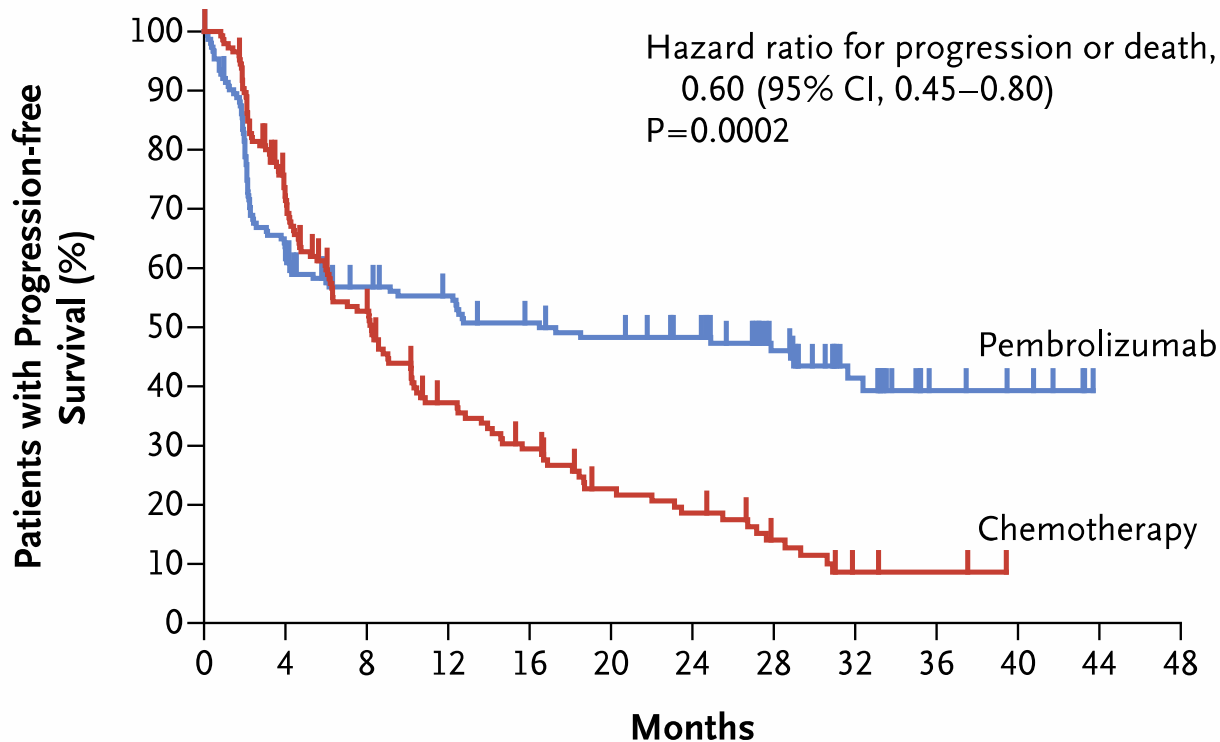
Translates into an OS benefit in these patients

Overall Survival



First Line Pembrolizumab in MSI high CRC versus Standard Chemotherapy

- 2 year Progression Free Survival of 48% v 18%%!!!



NEJM 2020

Take home on immunotherapy (so far)

- Definite role in microsatellite unstable (Lynch) colon cancer and other GI cancers
- **FDA Approval in:**
 - **MSI-high colorectal**
 - **third-line gastroesophageal with high PDL1**
 - **First-line hepatocellular carcinomas**
 - **Any line, any solid tumor that is MSI-high**



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Conclusions

- Colon cancer: keys are early detection, effective treatment, active surveillance, secondary prevention
- Pancreatic cancer: let's treat it as metastatic regardless of where the patient is on the spectrum of operability...but operate on as many patients as possible!
- Immunotherapy: incredible value in patients with MSI high GI cancers



Quiz

A patient is guaiac positive on exam in your clinic. You send the patient for colonoscopy and a mass is detected in the transverse colon. What next?

- a) CT scan of Chest/Abdomen/Pelvis for staging
- b) Surgical consultation for removal of the mass
- c) Check CEA level
- d) All of the above



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Quiz

A patient is guaiac positive on exam in your clinic, and on DRE you palpate a mass at 5cm. You send the patient for colonoscopy and a rectal mass is confirmed. What next?

- a) Referral to a multidisciplinary clinic for evaluation
- b) Rectal MRI
- c) Check CEA
- d) CT Chest/Abdomen/Pelvis for staging
- e) All of the above



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Quiz

What percentage of pancreatic cancer patients will have inherited the breast cancer gene?

- a) 5%
- b) 25%
- c) 50%
- d) 75%



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